REMARKS

Entry of the foregoing and reexamination and reconsideration of the above-identified application, as amended hereby, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks that follow, are respectfully requested.

Applicants acknowledge the withdrawal of the prior objections to the specification and to claims 1-12, based on informalities. Applicants also acknowledge that the rejection of claims 9, 15 and 26, pursuant to 35 U.S.C. § 112, second paragraph, has been overcome and that the prior rejections pursuant to 35 U.S.C. § 102(b) and § 103(a) have been withdrawn.

The specification is now objected to because of the presence of "en" on page 6, line 9. This has been corrected. Applicants also wish to draw the examiner's attention to changes to replace the word "blood" with "seric" and "serum" as appropriate in both the specification and claims. The French version of the priority application as filed recites "serum" and this was erroneously translated into "blood" and "blood proteins."

Claims 1, 8, 9, 19 and 24 are currently objected to because of minor typographical informalities. These have all been corrected. Claim 3 was objected to as being in improper dependent form for failing to further limit the claim from which it depended. While applicants respectfully disagree, the claim has been canceled hereby and thus the objection is moot.

Claims 25, 29, 30 and 33 are now rejected pursuant to 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants have amended claim 25 as the examiner suggested and thus the rejection should be moot.

Before discussing the individual references, applicants respectfully point out that nothing in the references applied teaches or suggests the methods claimed as none of the references teaches or suggests the idea of associating a particular species in a buffering solution with a particular

human serum constituent to be separated or ensuring that that additive, added to accomplish same, contains both a domain which will allow the association and another which will amend the behavior of the material when in an electric field when part of separation. The only way to arrive at that invention in view of the art is in hindsight using applicants' discovery and specification as a guide.

Claims 1-3, 7-10, 12, 13, 16-21, 23-25, 27, 29 and 33 have been rejected pursuant to 35 U.S.C. § 102(b) as allegedly anticipated by Lauer *et al.*, "Capillary Zone Electrophoresis of Proteins in Untreated Fused Silica Tubing," Anal. Chem. Vol. 58, pages 166-170 (1986) ("Lauer"). As that rejection will be applied to the claims as amended, applicants respectfully traverse. As to method claims 1, 20 and 21 (and the claims dependent therefrom), applicants note that, as amended, the claim specifies analyzing human biological samples. This is supported by the specification as filed at page 7, lines 8-10. The proteins separated by Lauer (see Table 1) appear to be exclusively of a non-human origin. Indeed, the proteins are purified proteins (see page 167, left column, under the heading "Reagents" where it is explained that pure proteins were dissolved in a buffer solution). Therefore, the process disclosed in Lauer cannot be understood as a process according to the invention where materials of separated and analyzed from human samples of a biological origin. On that basis alone, the claims are not anticipated. The claims as amended also recite a separate buffer and additive as discussed in more detail below. Lauer has no such disclosure and cannot anticipate these claims.

As to claims 24 and 25, as well as the claims that depend therefrom, claim 24 clearly recites (and claim 25 has been minorly amended to clarify) the need for both a buffer and an additive. The CHES buffer of Lauer even if it could act as suggested by the examiner in the claim method (which applicants vigorously dispute) does not describe the concurrent use of an

additive. This is not merely a matter of semantics. How can one in accordance with Lauer amend the buffering capacity without changing the ability of the buffer to affect human albumin separation? The answer is simple. It cannot. Buffering and buffering capacity are separate and distinct functions from the function of the additive which is believed to aggregate with the human albumin influencing its overall charge and affecting separation. By use of the present invention, one can add as much additive as necessary independent of buffering capacity and the type of buffer used. More fundamentally, however, the claim requires two elements and the art that the examiner relies on at this point cites, at best, only one of those two elements. Accordingly, it cannot anticipate the claims.

Moreover, claims 24 and 25 have additionally been amended to insert the word "linear" after "cholates." This term is literally supported in the specification as filed at page 6, line 16. By the examiner's statement contained in part 13 of the official action, the CHES buffer contains a cyclohexyl group and claim 25, as amended, now excludes that compound. This amendment has also been made to claim 29. Accordingly, applicants respectfully submit that Lauer does not anticipate the current claims as amended.

Claims 1-3, 7-10, 12-21, 23-25, 27, 29 and 33 stand rejected pursuant to 35 U.S.C. § 103(a) as allegedly being unpatentable over Lauer, when taken alone. As that rejection would be applied to the claims as amended, applicants respectfully traverse. Applicants note that Lauer does not teach separating serum proteins from human biological fluids as claimed in claims 1, 20, and 21. Indeed, as previously noted, Lauer uses already purified nonhuman proteins, not human biological samples. Second, Lauer does not teach or suggest the use of a separate buffer and additive. This is important not only for the reasons described previously with regard to the

independently adjusting buffering and the degree of separation by effecting the degree of hydrophobicity or charge in the additive and/or the amount of additive.

No — this distinction underlies a very significant difference which goes to the very core of the nonobviousness of the present invention. Specifically, the invention claimed in claims 1, 20, and 21 is a method and nothing in Lauer teaches that method. Nothing in Lauer recognizes the need for the use of a particular additive material having a hydrophobic domain and an anionic charge as a means of associating with specific human biological proteins from serum. All Lauer teaches or suggests to a person or ordinary skill in the art is the use of a buffer in capillary electrophoresis.

It in no way enlightens one of ordinary skill in the art that advantages can be obtain by the use of specific additive agents, in addition to a buffer, nor does it give any teaching as to the fact that the additive agents must have specific attributes and be tailored for a specific purpose. Even if the buffer described in Lauer could in any way exert an influence as discovered by applicants, there is no teaching, suggestion, or motivation for same and the only way that one of ordinary skill in the art could glean such a teaching is by the impermissible use of hindsight.

That is, they would use the teaching of the claimed invention against the inventor as if it were in the prior art. Looking at Lauer alone, without the teachings of the invention, it would not be possible for one or ordinary skill in the art to be possessed of the invention and therefore, the claimed invention is not obvious therefrom. Moreover, nothing in Lauer teaches or suggests an invention in accordance with claims 24, 25, or the claims dependent therefrom, namely, a solution that contains a buffering system that contains both a buffer and an additive as claimed. This is certainly true in connection with claims 24 and 25, which, as amended, also exclude the buffer

cited by the examiner. Moreover, Lauer fails to teach or suggest a capillary electrophoresis process using human serum proteins.

Claim 5 has been rejected pursuant to 35 U.S.C. § 103(a) as allegedly being unpatentable over Lauer when taken in view of Karger, U.S. Patent No. 4,778,909 ("Karger"). However, it is respectfully submitted that the combination fails to teach or fairly suggest the subject matter which is deficient from Lauer as described above. Accordingly, even if combinable, which they are not, the presently claimed invention would still be unobvious.

Moreover, the Patent Office has failed to establish a *prima facie* case supporting the combination of these two references. Karger deals with a column or silica-based chromatographic support based separation technology. It is not an electrophoresis process and is not analogous. Moreover, according to the examiner, one looking at Karger would think it obvious at the time the invention was made to use human tranferrin or BSA as protein in Lauer's capillary zone electrophoresis because the proteins have a certain pI value within the range of value set forth in Table 1 of Lauer. With all due respect, so what? It is not enough to merely find the missing element from a primary reference in a secondary reference and note that they might have, completely divorced from anything else, a similar property. There must be a teaching, suggestion, or motivation for one using an electrophoretic device and technique such as suggested in Lauer to look to a silicon based chromatography application and decide that, based on that completely disparate teaching, it would be obvious to attempt to separate human serum albumin using its own technique. Quite simply, that rationale is insufficient. On what basis would that person of ordinary skill in the art select that, and only that teaching from Karger, ignoring all of the

rest? Certainly there is nothing in Lauer to suggest this modification.

Moreover, Karger teaches BSA, which is bovine serum albumin, not human serum albumin and, as noted before, neither reference, taken alone or in combination, teaches the use of a buffering system including both a buffer and an additive.

Claim 22 has been rejected pursuant to 35 U.S.C. § 103(a) as allegedly being unpatentable over Lauer taken in view of Ohmura *et al.*, U.S. Patent No. 5,521,287 ("Ohmura"). Again, applicants respectfully traverse. Ohmura does not overcome the deficiencies of Lauer as noted earlier. Ohmura is drawn through the purification of albumin obtained by gene modification, a nonanalogous problem solved by a totally different separation process. The purified HCA in accordance with Ohmura which is to be purified from a host-related substance includes only contaminants resulting from the production process which are totally different than separation from other serum-based proteins of a human biological sample. Nothing in this reference teaches or suggests electrophoresis or that its teachings may be applied to electrophoresis. Indeed, Ohmura describes adjusting the ionic strength of HAS dissolution buffing system which, if anything, when combined with Lauer teaches modifying ionic strength but not modifying charges to be associated with a particular constituent.

Claims 24, 25, 27, 29, and 33 also stand rejected pursuant to 35 U.S.C. § 102(b) as allegedly being anticipated by Alter *et al.*, U.S. Patent No. 5,753,094 ("Alter"). As that rejection would be applied to the claims as amended, applicants again respectfully traverse. It is respectfully noted that TES as relied upon by the Patent Office would not have a hydrophobic domain as described in accordance with the present invention. Instead, TES would be generally hydrophilic. It therefore could not have a hydrophobic interaction with human albumin. In addition, according to claim 24, the buffer system has a pH of

between 9 and 11. However, TES is added to a buffer having a pH of about 7.

As to claim 25, it is noted that TES is, in addition, not a linear alkyl sulfonate or any of the other classes of materials claimed. Accordingly, applicants respectfully submit that the claims are not anticipated by Alter.

Claims 24, 25, 27, 29 and 33 have been rejected pursuant to 35 U.S.C. § 102(b) as allegedly being anticipated by Keo *et al.*, U.S. Patent No. 5,599,433 ("Keo"). Claims 1, 3-5, 7-10, 12-21, 20-25, 27, 29, and 32 stand rejected pursuant to 35 U.S.C. § 103(a) over Keo. Applicants again respectfully traverse. Keo suggests the ability to separate hemoglobin and related proteins, not human serum proteins. Furthermore, it does not disclose the ability to separate serum proteins such as albumins and globulins. And nothing in Keo appears to teach the additives as currently claimed including the recite linear alkyl sulphonates.

Moreover, nothing in Keo teaches or suggests the method of the claimed invention. Nothing teaches the use of a buffering system that comprises both a buffering agent and a material which is, by design, added at added in sufficient quantity to allow it to associate with a particular constituent of human serum and aid in separation. No one could read Keo and glean that from amongst the myriad of possible things that could be used as described in Keo, one should select for use only those "additives" which would be associative with human albumin and would have the correct negative charge so as to effect and assist in separation. Even if Keo did suggest, in the abstract, a buffer system comprising something that could (only after the present application has been read) possibly provide such benefit is not a substitute for teaching, suggesting, or motivation to select this from the various teachings of Keo.

Looking at Keo alone, one would have no teaching, suggestion, or motivation to pick a particular buffer or buffer

system to meet the goals set forth for the first time in the instant application. As such, it cannot anticipate or render obvious the claimed invention. Moreover, it is well-known in the industry that capillary electrophoresis is a highly discriminating and highly specific technique. The fact that capillary electrophoresis process is so highly sensitive in terms of separating a particular constituent is of little guidance or assurance of the ability to separate others. The biological materials to be separated in accordance with the present invention are indeed different from those suggested in Keo and those of ordinary skill in the art would find this to be highly significant in terms of considering whether or not Keo's teaching would be broadly applicable to the claimed invention.

Applicants also respectfully submit that in accordance with Keo, borates are used in the separation of glycocelated Hbs from nonglycocelated Hbs. However, in the separation in accordance with Keo, the borate is used as a complexant. However, in accordance with the present invention, borates, if used at all, are used as the buffer. To the extent that something within Keo could be argued to be the "additive" in accordance with the present invention. Keo points to the wrong material. As to claim 25, the claims dependent therefrom, is also respectfully noted. The claim has been amended to exclude the material identified by the examiner.

Claims 24 and 25 have been rejected pursuant to 35 U.S.C. § 103(a) as allegedly being unpatentable over Ogawa, U.S. Patent No. 4,769,408 ("Ogawa"). Applicants respectfully traverse. It is clear from the claims themselves as well as the complete disclosure of the invention that the formulation's buffering systems of the present invention are solutions. They are not gels and do not contain gelling agents. Moreover, it is believed by applicants that Ogawa does not fairly teach or suggest a buffer system as claimed in the claims as amended and particularly as reflected in claims 25, 27-30 or 33.

Claims 27, 29, and 33 are rejected pursuant to 35 U.S.C. § 103(a) as allegedly being unpatentable over Ogawa further in view of Mullis, U.S. Patent No. 4,965,188 ("Mullis"). It is noted, however, that nothing in Mullis overcomes the deficiencies identified in Ogawa. And indeed, it is not clear that one could even combine these references in view of their different physical states. Moreover, Mullis involves the assaying of enzyme activity with the reaction buffer together with activated salmon sperm DNA. This is quite apart from capillary electrophoresis buffer system and the examiner cited no reason of record why these would be combinable in accordance with the present invention. Moreover, as amended, claim 25 has been limited such that the alkyl sulfonate buffers are linear. This is not taught by either reference.

Finally, claims 24 and 25 and 27-30 are rejected pursuant to 35 U.S.C. § 103(a) as allegedly being unpatentable over Bellon *et al.*, U.S. Patent No. 5,928,484 ("Bellon") in view of Keyes, U.S. Patent No. 4,714,677 ("Keyes") and Bloebaum *et al.*, U.S. Patent No. 4,872,865 ("Bloebaum"). With all due respect, the fact that the Patent Office must rely on three separate references to reject these claims, speaks volumes as to whether or not they are indeed obvious. Bellon fails to teach the pH range of the compositions of the present invention. The TRIS buffer described is known to have a pH of between 6.6 and 8.8. And there is no reason to combine Bellon with Bloebaum or Keyes to change this fact and there is no teaching or suggestion or motivation to do so. Bloebaum further concerns conforming various solutions to normal physiology and Keyes concerns modification of protein. None of these are within the technical field of separation chemistry let alone, capillary electrophoresis. Absent more, one of ordinary skill in the art would not seek to combine these references as taught.

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

If, however, for any reason the examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: October 27, 2005

Respectfully submitted,

By _____

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